DESCRIPTION

POLYOL COMPOUNDS, THEIR PRODUCTION AND USE

This application is a 371 of PCT/JP00/00023 filed January 6, 2000.

TECHNICAL FIELD

The present invention relates to a polyol, a method of its production, and its use. More particularly, the invention relates to a bioactive compound of use as a medicine, for as a preventing and treating drug for diseases such as gastric ulcer and duodenal ulcer, and an anti-Helicobacter pylori agent containing the said compound.

BACKGROUND ART

Being a member of the group of bacteria doing harm in the gastrointestinal tract, Helicobacter pylori is a gram-negative microaerophile belonging to the genus Helicobacter and, as suggested, may be a major factor in the recurrences of gastritis, duodenal ulcer and stomach ulcer.

For the treatment of various diseases associated with Helicobacter pylori infection, chemotherapy such as a two-drug combined therapy using a bismuth drug and an antibiotic or a three-drug combined therapy using a bismuth drug, metronidazole (US Patent 2,944,061), and either tetracycline (e.g. US Patent 2,712,517) or amoxicillin (US Patent 3,192,198) is being practiced today. The ternary therapy consisting of a gastric proton pump inhibitor, amoxicillin, and clarithromycin has also been found to be effective (Gut, 1995, 37 (Supplement 1) : A365) (Gastroenterology, 1996, 110 : A171). Such drugs as bismuth drugs, antibiotics, and metronidazole are all administered by the oral route.

Referring to polyols, PCT International Patent Application Publication No. WO93/06838 and Acta Chemical Scandinavica B 36, 515-518 (1982) disclose

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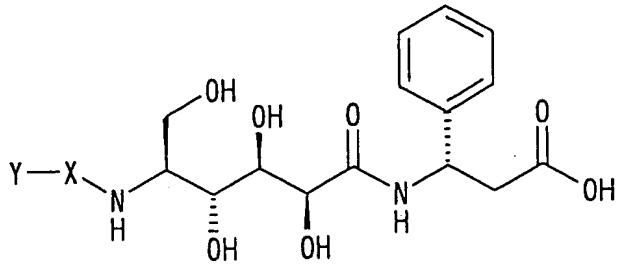
CLAIMS

1. (Amended) A compound of the formula:



(I)

wherein X is L-serine residue, L-asparagine residue or (S)-2-aminobutyric acid residue and Y is α-L-amino acid residue, or ~~its~~ a salt thereof.

2. A compound as claimed in claim 1, wherein X is (S)-2-aminobutyric acid residue.

3. A compound as claimed in claim 1, wherein Y is norvaline residue, isoleucine residue or methionine residue.

4. A compound as claimed in claim 1, which is (S)-3-[(2S,3R,4R,5S)-5-(L-norvalyl-(S)-2-aminobutyryl)amino-2,3,4,6-tetrahydroxyhexanoyl]amino-3-phenylpropionic acid or its salt.

5. A compound as claimed in claim 1, which is (S)-3-[(2S,3R,4R,5S)-5-(L-isoleucyl-(S)-2-aminobutyryl)amino-2,3,4,6-tetrahydroxyhexanoyl]amino-3-phenylpropionic acid or its salt.

6. A pro-drug of the compound claimed in claim 1.

7. (Amended) A pharmaceutical composition which contains the compound claimed in claim 1 or its pro-drug and a pharmaceutically acceptable additive.

8. A pharmaceutical composition as claimed in claim 7, which is an anti-Helicobacter pylori agent.

9. A pharmaceutical composition as claimed in claim 8, which is a preventing and treating agent of Helicobacter pylori infectious disease.

10. A pharmaceutical composition as claimed in claim 9, wherein Helicobacter pylori infectious disease is gastric or duodenal ulcer, gastritis, gastric cancer or gastric MALT lymphoma.

11. A pharmaceutical composition as claimed in claim 7, which

is a gastric mucosa adhesive pharmaceutical composition.

12. (Amended) A pharmaceutical composition ~~as claimed in claim 11, wherein~~ which is a gastric mucosa adhesive pharmaceutical composition ~~contains~~ comprising (a) a compound as claimed in claim 1, (b) a lipid and/or a polyglycerol fatty acid ester and (c) a viscogenic agent capable of being viscous with water.

13. A pharmaceutical composition as claimed in claim 12, wherein (c) the viscogenic agent is an acrylic polymer.

14. A pharmaceutical composition as claimed in claim 12, which further contains (d) a material which swells the viscogenic agent.

15. A pharmaceutical composition as claimed in claim 14, (d) the material which swells the viscogenic agent is curdlan and/or a low-substituted hydroxypropylcellulose.

16. A pharmaceutical composition which contains both of a compound as claimed in claim 1 or its pro-drug and the other antibacterial agent and/or an antiulcerative agent.

17. A method for treating or preventing a mammal suffering from a Helicobacter pylori infectious disease, which comprises administering an effective amount of a compound according to claim 1 or its pro-drug optionally together with a pharmaceutically acceptable carrier, diluent or excipient, to a patient suffering from the disease.

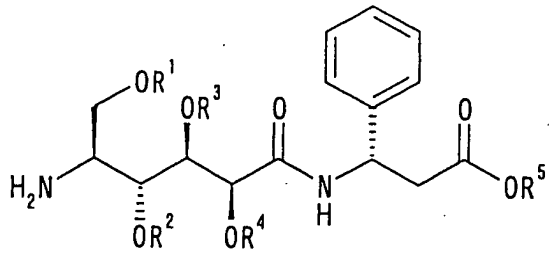
18. A method as claimed in claim 17, wherein Helicobacter pylori infectious disease is gastric or duodenal ulcer, gastritis, gastric cancer or gastric MALT lymphoma.

19. (Amended) ~~Use of the compound according to claim 1 or its pro-drug for~~ A method for manufacturing ~~of~~ a pharmaceutical composition for a Helicobacter pylori infectious disease, which comprises mixing the compound according to claim 1 or its pro-drug with a pharmaceutically acceptable additive.

20. (Amended) ~~Use~~ the method as claimed in claim 19, wherein the composition is for treating or preventing a Helicobacter pylori infectious disease.

21. (Amended) ~~Use~~ the method as claimed in claim 20, wherein the Helicobacter pylori infectious disease is gastric or duodenal ulcer, gastritis, gastric cancer or gastric MALT lymphoma.

22. (Amended) A method for producing a compound claimed in claim 1, which comprises reacting a compound of the formula:



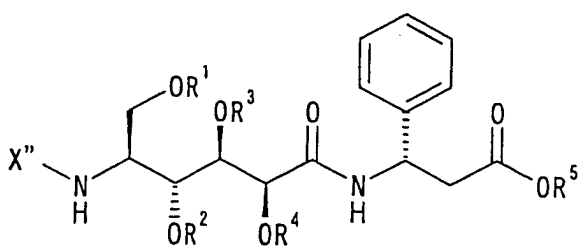
(II)

wherein R^1, R^2, R^3 and R^4 are independently a protecting group for hydroxy group or a hydrogen atom, and R^5 is a protecting group for carboxyl group or a hydrogen atom, or a salt thereof or a reactive derivative thereof at the amino group, with a compound of the formula:

$$Y'—X'—OH \qquad (III)$$

wherein X' is L-serine residue which may be protected, L-asparagine residue which may be protected or (S)-2-aminobutyric acid residue, and Y' is α-L-amino acid residue which may be protected, or a salt thereof or a reactive derivative thereof at the carboxyl group, if necessary, followed by removing the protecting group.

23. (Amended) A method for producing a compound claimed in claim 1, which comprises reacting a compound of the formula:



(IV)

wherein X" is L-serine residue which may be protected, L-asparagine residue which may be protected or (S)-2-aminobutyric acid residue, R^1, R^2, R^3 and R^4 are independently a protecting group for hydroxy group or a hydrogen atom, and R^5 is a protecting group for carboxyl group or a hydrogen atom, or a salt thereof or a reactive derivative thereof at the amino group, with a compound of the formula:

$$Y'—OH \qquad (V)$$

wherein Y' is α-L-amino acid residue which may be protected, or a salt thereof or a reactive derivative thereof at the carboxyl group, if necessary, followed by removing the protecting group.